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Trisomy 15 Mosaic Derived From Trisomic Conceptus: Report of a Case and a Review

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We report on a fetus with 47,XX,+15 chromosome abnormality detected on chorionic villus sampling (CVS). The pregnancy was terminated at 15.5 weeks of gestation and chromosome analysis done on amniocytes and fetal tissues showed a karyotype 46,XX/47,XX,+15. Autopsy showed multiple abnormalities. Short-arm polymorphisms of the three number 15 chromosomes were highly informative in the delineation of parental origin and the stage of meiotic error. Using fluorescent in situ hybridization (FISH) with D15Z1 and a chromosome 15 painting probe, in addition to DA/DAPI and G-banding, we were able to show that the trisomic conceptus was derived through maternal meiosis I error. The trisomic state was then partially corrected by the loss of one of the two maternal 15s resulting in mosaicism without uniparental disomy (UPD).

Striking differences in the proportion of trisomic cells in kidneys, blood, intestine, and skin, and lower proportions of trisomic cells in transformed and frozen than in fresh tissues, illustrate the continuing cell selection in this fetus in favour of the normal cell line.

Trisomy 15 conceptions are usually aborted spontaneously in the first trimester of pregnancy. The longer survival of this fetus is most probably the result of a chromosome 15 loss from the trisomic zygote. To the best of our knowledge, the presence of this lethal trisomy has been reported in only five liveborn infants, and in five fetuses including the present case, it was detected prenatally and the pregnancies were terminated.

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INTRODUCTION

The incidence and timing of pregnancy losses in humans have been reviewed by Simpson [1990]. According to ultrasonographic data, most losses occur before the 8th or 9th week of gestation, 2 to 3 weeks prior to expulsion and clinical recognition of the pregnancy loss. While conceptions with monosomies and unbalanced structural aberrations may not survive the implantation stage, trisomies including trisomy 15 are usually lost following implantation.

Like other acrocentric trisomies, trisomy 15 in spontaneous abortions is mainly observed in nonmosaic form [Hassold, 1982; Warburton et al., 1991]. The mean gestational age of 51 trisomy 15 fetuses ascertained in the New York City survey of spontaneous abortions was 12.54 ± 2.81 weeks [Warburton et al., 1991; Warburton, personal communication]. It is very rare that conceptions carrying this trisomy survive longer to be found at midtrimester amniocentesis or in liveborns.

Chromosome 15 loss from a trisomic zygote was first demonstrated in 1992 [Purvis-Smith et al., 1992; Cassidy et al., 1992]. In these two cases trisomy 15 was found at CVS, a diploid karyotype at amniocentesis, and Prader-Willi syndrome (PWS) at birth due to maternal UPD. Chromosome 15 loss was subsequently demonstrated in two cases of trisomy 15 mosaicism, one in a fetus [Rocklin et al., 1994], and one in a liveborn infant [Milunsky et al., 1994]. In both cases maternal UPD was found in a diploid cell line. We report on a chromosome 15 loss in a case of mosaicism who had a chromosome 15 contribution from both parents in a diploid cell line. Clinical consequences of the chromosome 15 loss and the relevance to prenatal diagnosis are discussed.

CLINICAL REPORT

Family History

A 37-year-old woman was referred for prenatal diagnosis because of advanced maternal age (AMA). She

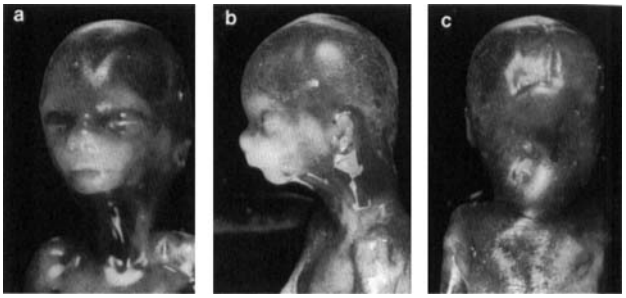

Fig. 1. Fetus after genetic termination at 15.5 weeks of gestation. **a:** Facial appearance—front. **b:** Facial appearance—profile. **c:** Back of head.

had three spontaneous abortions and one liveborn male prior to the pregnancy with trisomy 15. Subsequently, she had another spontaneous abortion and a normal female. Her chromosomes and those of her husband appeared normal at the 400-band level.

The trisomic pregnancy had been uneventful. Fetal U/S done at CVS (11 weeks and 1 day) showed a single intrauterine pregnancy with crown-rump length of 45 mm with no apparent abnormalities.

Cytogenetic Data

Ten of ten cytotrophoblast cells and 29 of 30 cultured mesenchymal core cells showed 47,XX,+15 (Table I). One cell with only two 15s was thought to represent a random chromosome loss since six other cells also showed aneuploidy for single chromosomes. Therefore, the karyotype was considered to be fully trisomic. Amniocentesis was performed at 13 weeks gestation. Mosaicism was detected, with 36% of the cells being trisomic. The pregnancy was terminated at 15.5 weeks and mosaicism (29% trisomic cells) was confirmed in a second amniotic fluid sample. When fetal tissues were examined, different proportions of trisomic cells were found in various tissues. At least 50 cells were examined from each tissue.

Pathology

The female fetus at 15.5 weeks gestation weighed 110 g (normal = 91–140 g), crown-rump length was 12.5 cm (normal = 11.5–12.8 cm), head circumference 12.2 cm (normal = 11.2–13.8 cm), and chest circumference 11.2 cm (normal = 9.5–12.0 cm). Craniofacial ab-normalities included brachycephaly with redundant skin over the nuchal area. The nasal bridge was depressed with a small pointed nose and anteverted nostrils. The philtrum was long and the palate intact. Retrognathia and small ears were present (Fig. 1). The chest was normal and no abnormalities of lungs or cardiovascular system were seen. The umbilical cord vessels and insertion were normal and the gastrointestinal and urogenital systems were normal, apart from apparent clitoromegaly. The palmar creases were normal. Histopathological examinations of the placenta, lungs, heart, liver, kidneys, small and large intestine, thymus, and ovaries were normal. Skeletal films were normal.

Study of Chromosome Heteromorphisms

To establish the origin of the extra chromosome, cytogenetic heteromorphisms of the three number 15 chromosomes were compared with those of number 15 chromosomes in parental cells (Fig. 2). Two of the three chromosome 15 short arms were very similar to the short arms of the two maternal 15s, one of which was of a medium size and the other one very small. The third chromosome 15 was highly heteromorphic with an extremely large paternally derived short arm region. The paternal 15 not present in fetal cells was morphologically quite distinct, with a short arm larger than maternal 15s and considerably smaller than the paternal 15 passed to the fetus. The differences in the short arm size were particularly well-defined when FISH was performed with D15Z1 probe labelled by biotin [Oncor catalog number P5034 (not shown)] or with DA/DAPI banding (Fig. 2). These differences were also evident when FISH was performed with a chromosome 15 painting probe labelled by biotin or digoxigenin [Oncor catalog numbers P5216-BIO and P5216-

TABLE I. Trisomic Cells in Fresh and Frozen Tissues

	Fresh tissue		Frozen tissue	
Tissue	Number of cells	Number of trisomic cells (%)	Number of cells	Number of trisomic cells (%)
Pre-termination				
Cytotrophoblast	10	10 (100)	—	—
Villus mesenchyme	30	29 (96.7)	—	—
Amniotic fluid I	50	18 (36)	—	—
Amniotic fluid II	31	9 (29)	—	—
Post-termination				
Heart blood	51	12 (23.5)	253	0 (0)
Left kidney	50	3 (6)	—	—
Right kidney	54[a]	5 (9.2)	—	—
Intestine	54	24 (44.4)	91	7 (7.7)
Skin	54	23 (42.6)	226	8 (3.5)

[a]Two cells were 45,X.

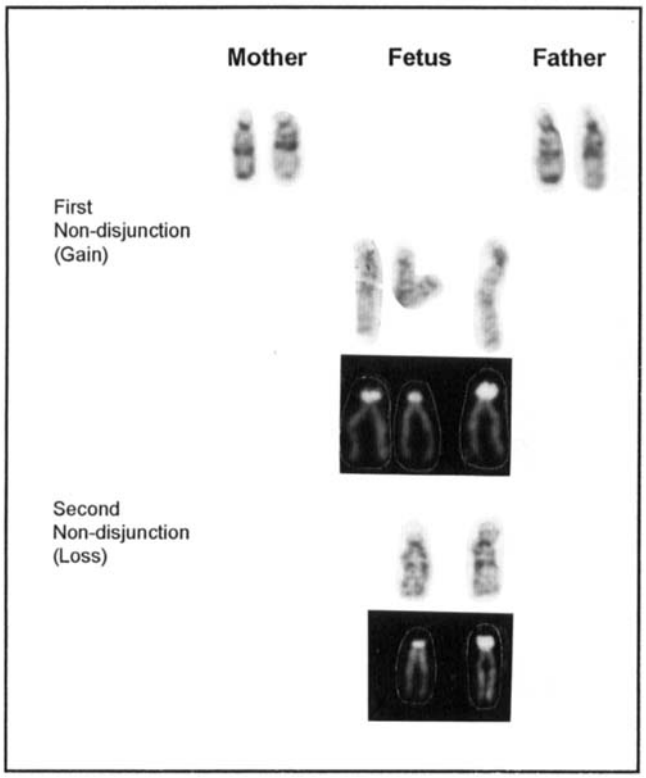

Fig. 2. Partial karyotypes with chromosome 15 heteromorphisms from the mother (G-banding), father (G-banding), and fetus (G-banding and DA/DAPI). The chromosome on the right in trisomic cells is paternally derived; two others are maternally derived. The chromosome on the left was lost in the second non-disjunction event leaving the two 15s, one with exceptionally large paternally derived short arm, and one with exceptionally small maternally derived short arm, in the diploid cell line.

DIG, respectively (not shown)], or with G-banding (Fig. 2). The diploid cells from both amniotic fluid samples and from fetal tissues had the maternally derived chromosome 15 with the small short arm and the paternally derived highly heteromorphic 15. They did not have the maternally derived 15 with a medium size short arm, which was present in all trisomic cells.

Further Studies on Frozen Cells

Fetal tissues and heart blood lymphocytes transformed with Epstein-Barr virus (EBV) were stored in liquid nitrogen at −196°C. When these were recultured a few months later and screened using a chromosome 15 painting probe, G-banding, and DA/DAPI staining, only diploid cells were detected in heart blood lymphocytes (N = 129). A second recultured vial (another flask) of the same transformed blood lymphocytes also showed no trisomic cells (N = 124) (see Table I and Fig. 3). Two of the frozen tissues with the highest proportions of trisomic cells were then recultured. Only 7 of 91 frozen intestine cells were trisomic (7.7%) compared to 44.4% in the original intestine culture. Only eight of 226 skin fibroblasts were trisomic (3.5%) compared to 42.6% in the original skin culture.

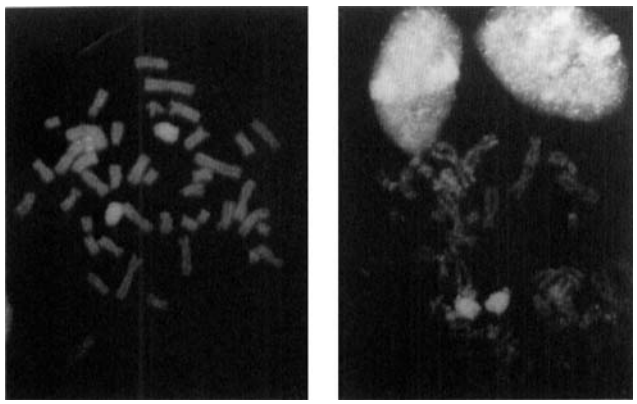

Fig. 3. Metaphase spreads of transformed blood lymphocytes after freezing and reculturing examined by the digoxigenin-labelled chromosome 15 painting probe and FISH. Note that only two number 15 chromosomes are present in each cell.

DISCUSSION

Survival and Clinical Features of Trisomy 15 Conceptions

Although conceptions with trisomy 15 are not rare, only a few survive to birth. Most of them have been ascertained in karyotyped spontaneous abortions [Warburton et al., 1991; Hassold et al., 1984; Eiben et al., 1990]. Trisomy 15 has been described in only five liveborn infants and, in five fetuses including the present case, it was detected prenatally and the pregnancies were terminated. Table II presents a listing of all reported cases including some cases with confined placental mosaicism (CPM), since they may also be derived from trisomic conceptions. The sex, gestational age, and maternal age at ascertainment are shown.

Despite gross malformations usually observed in newborns with trisomy 15, there are no consistent manifestations that would make this trisomy recognizable at birth. Tables III and IV summarize the clinical findings in newborn infants and fetuses presented in case reports. Coldwell et al. [1981] reported on a liveborn female delivered at term with multiple congenital abnormalities and severe growth retardation. The infant died on the fourth day of life of intractable heart failure. Trisomy 15 was found in all 100 cells examined from peripheral blood lymphocytes, the only tissue studied. Stallard and Sommer [1989] described a 2-year-old male without major phenotypic abnormalities at birth. Peripheral blood and skin had 45,X cells with only two number 15 chromosomes, whereas 45,X/47,XY,+15 mosaicism was found in both testes. Kuller and Laifer [1991] presented a case of a female conceived after in vitro fertilization and born prematurely at 33 weeks gestation after rupture of membranes. The pregnancy was complicated by nonimmune hydrops fetalis with polyhydramnios and fetal ascites. The infant died 9 hours after birth. Trisomy 15 was found in 20 cells examined from the peripheral blood; no other tissues were studied. Lahdetie and Lakkala [1992] described mosaicism for trisomy 15 ascertained at midtrimester amniocentesis. Although a repeat amniocen-

TABLE II. Trisomy 15 From Different Sources of Ascertainment[a]

Reference	Chromosome aberration	Number of cases	Sex M	Sex F	Gestation at birth or abortion (weeks)	Maternal age	Source of tissue	Follow-up tissues	Outcome
Markovic et al., present case	+15 Mosaic	1		1	15.5	37	CVS	A, FT	TA, Abnormal
Milunsky et al., 1994	+15 Mosaic	1		1			Amnio IIId. trim.	LB (skin lung)	Abnormal
Rocklin et al., 1994	+15 Mosaic	1					Amnio	FT	TA, Abnormal
Sundberg et al., 1994	+15 Mosaic	1		1	20	35	Amnio 12 weeks	Cordo, FT	TA, Abnormal
Warburton et al., 1991									
Warburton, personal communication	+15	52	26	26	12.54 ± 2.81	33.6 ± 6.38	SA	—	Abnormal
Wang et al., 1993	+15 Mosaic	1		1	—	—	CVS	FT	TA, no info
Bennett et al., 1992a	+15 Mosaic	1	1		>16	41	Cordo	—	TA, Abnormal
Teshima I, Gardner A, Hutton, E, unpublished	+15 Mosaic	1		1	20	36	Amnio	—	TA, Abnormal
Ledbetter et al., 1992	+15	3			—	—	CVS	—	2 CPM
Purvis-Smith et al., 1992	+15 Mosaic	1	1		Term	—	CVS	A, LB (blood)	CPM, PWS
Cassidy et al., 1992	+15	1		1	Term	43	CVS	A, LB (blood)	CPM, PWS
Lahdetie and Lakkala, 1992	+15 Mosaic	1		1	37 + 2	40	Amnio	Umbil. cord	Abnormal
Kalousek et al., 1991	+15 Mosaic	1		1	38	—	CVS	Term placenta	CPM, IUGR
Kuller and Laifer, 1991	+15	1		1	33	30	LB	—	Abnormal
Ohno et al., 1991	+15	2	1	1	—	—	SA (CVS)	—	No info
Eiben et al., 1990	+15	7			10.9	—	SA (CVS)	—	No info
Breed et al., 1990	+15	1		1	—	—	CVS	—	SA, CPM
Stallard and Sommer, 1989	45,X/47,XY,+15	1	1		—	23	LB	—	Mild abnormalities
Schulze et al., 1987	+15 Mosaic	1		1	—	—	CVS	FT	CPM
Hogge et al., 1986	+15 Mosaic	1		1	—	—	CVS	—	CPM
Simoni et al., 1986	+15	4		4	8.2–9	39–43	CVS	—	Unclear
Lin et al., 1985	t(15q15q)	1		1	10	27	SA	—	No info
	+15	3	1	2	9.5–10	24–33	SA	—	No info
Mikkelsen, M., 1985	+15	2		2	—	—	CVS	—	No info
Karkut et al., 1985	+15	1	1		—	—	CVS	—	No info
Hassold et al., 1984	+15	16	11	5	10.7–17	35.6+	SA	—	No info
Gimelli et al., 1983	+15 Mosaic	1		1	24	—	Amnio	FT	TA, Abnormal
Coldwell et al., 1981	+15	1		1	Term	—	LB	—	Abnormal
Kajii et al., 1980	+15	11	4	7	—	—	SA	—	No info

[a] A, amniotic fluid; amnio, amniocentesis; cordo, cordocentesis; CPM, confined placental mosaicism; CVS, chorionic villus sampling; LB, liveborn; PWS, Prader-Willi syndrome; SA, spontaneous abortion; TA, therapeutic abortion; FT, fetal tissue; IUGR, intrauterine growth retardation.

TABLE III. Clinical Findings in Liveborns With Trisomy 15 and Trisomy 15 Mosaicism

	Coldwell et al., 1981	Stallard and Sommer, 1989	Kuller and Laifer, 1991	Lähdetie and Lakkala, 1992	Milunsky et al., 1994
Sex	F	M	F	F	F
Karyotype	+15	45,X/47,XY,+15	+15	+15 mos.[d]	+15 mos.[d,e]
Prenatal findings	IUGR	NA	Polyhydramnios, ascites, pleural effusion, breech presentation	IUGR Oligohydramnios breech presentation	IUGR
Reason for referral	MCA	Devel. delay	MCA	AMA	IUGR
Survival	4 days	>2 years	9 hours	13 days	6 weeks
Hypotonia	+	NR	NA	NR	NR
Growth retardation	+	+	–	+	+
Developmental delay	NA	+	NA	NA	NR
Craniofacial abnormalities	+	+	–	–	+
Skeletal abnormalities	+[a]	–	–	–	+
Limb abnormalities	+[b]	–	–	–	+
Rib abnormalities	+[c]	–	–	–	NR
Heart defects	+	–	–	+	+
CNS abnormality	NR	–	+	–	+
Anteriorly placed anus	+	–	–	–	NR

[a] Hypoplastic right clavicle, bilateral abnormal acetabuli, fusion of cervical vertebral arches.
[b] Bilateral talipes equinovarus, dislocated hips.
[c] Eleven pairs of ribs, left ribs deformity.
[d] Trisomy 15 mosaicism was found in amniocytes, patient's blood karyotype was normal.
[e] Skin chromosome analysis showed Trisomy 15 Mosaicism. MCA, multiple congenital abnormalities; IUGR, intrauterine growth retardation; NA, not applicable; NR, not reported; AMA, advanced maternal age.

tesis confirmed trisomy 15 mosaicism and ultrasound examination revealed IUGR, the parents opted to continue the pregnancy. The cord blood sample at birth had a normal karyotype, while umbilical cord, placenta, and fetal membranes had various degrees of trisomy 15 mosaicism. In addition to growth retardation, this newborn had multiple heart defects and hypoplasia of the left heart. The infant died 13 days after birth. A postmortem skin sample failed to grow, so confirmation of mosaicism was not possible. Milunsky et al. [1994] reported mosaicism for trisomy 15 at amniocentesis performed in the third trimester of pregnancy after IUGR was suspected on ultrasound examination. The liveborn infant was a female with multiple abnormalities including multiple heart defects, and died at 6 weeks of cardio-respiratory complications. Blood chromosomes were normal, but trisomy 15 mosaicism was confirmed in skin and lung tissue, and maternal UPD for chromosome 15 was discovered in the diploid cell line.

Maternal Age and the Source of the Chromosome Error

A close association between increased maternal age and trisomy was noted in the late 60s and early 70s when it was suggested that a large proportion of trisomy 21 mosaics may originate from a meiotic segregation error followed by a "normalizing" mitotic error [Richards, 1968, 1969, 1974]. Current data on trisomy 15 indicate that this trisomy is also closely associated with an increased mean maternal age [Hassold and Takaesu,

TABLE IV. Clinical Findings in Fetuses With Trisomy 15 Mosaicism[a]

	Gimelli et al., 1983	Bennett et al., 1992a	Sundberg et al., 1994	Rocklin et al., 1994	Markovic et al., present case
Sex	F	M	F	–	F
Karyotype	+15 mos.	+15 mos.	+15 mos.	+15 mos.	+15 mos.
Prenatal findings	NR	NR	Echodense nodules protruding into the amniotic cavity (transient), cardiac abnormality	NR	normal u/s
Reason for referral	AMA	AMA	AMA	AMA + Hist. of Tris. 21	AMA
Survival	TAB 24*	TAB >16*	TAB 20*	TAB 20*	TAB 15.5*
Growth retardation	–	–	–	–	–
Craniofacial abnormalities	+	+	NR	–	+
Limb abnormalities	+	+	–	–	–
Rib abnormalities	+	–	–		–
Heart defects	+	–	+	–	–
Accessory spleen	–	+	–	–	–
GI abnormality	+	–	–	+	–

[a] TAB, Therapeutic-abortion; *, weeks gestation; AMA, advanced maternal age; NR, not reported; GI, gastrointestinal; u/s, ultrasound.

1989; Hassold et al., 1992; Zaragoza et al., 1994]. In 52 spontaneously aborted trisomy 15 conceptions from a New York City survey of spontaneous abortions [Warburton, personal communication, unpublished], the mean maternal age was 33.6 ± 6.38 years, while the mean maternal age of spontaneously aborted conceptions with normal karyotypes (N = 1981) from the same region [Warburton et al., 1991] was 27.2 years. In our case the mother was age 37 and the father was 35.

Parental origin of non-disjunction has been summarized by Hassold et al. [1992] and Zaragoza et al. [1994]. In an analysis of a small number of published trisomy 15 cases, Hassold showed that non-disjunction occurred at maternal meiosis in six cases (75%), and at paternal meiosis in two cases (25%). The mean maternal age of the cases with the maternal meiotic error was 37.3 years, which is significantly higher than the mean maternal age (26.0 years for live births and 27.0 years for chromosomally normal spontaneous abortions) in control populations studied by Hassold and Jacobs [1984]. Out of 14 spontaneously aborted conceptions with trisomy 15, Zaragoza et al. [1994] found that non-disjunction occurred at maternal meiosis in 12 (86%), and at paternal meiosis in 2 (14%) cases. Maternal ages of those with a maternal meiotic error were between 34 and 42 years, while of the two with a paternal meiotic error were 32 and 34 years.

Robinson et al. [1991] were first to note that PWS patients with maternal UPD(15) also have increased parental ages. Based on a study of molecular markers Robinson et al. [1993a,b] concluded that a large proportion of maternal disomy 15 cases arose from maternally derived trisomic conceptions.

Non-disjunction of acrocentric chromosomes has traditionally been studied by cytogenetic heteromorphisms on the short arm, and more recently by DNA heteromorphisms in the proximal long arm. A comparison of cytogenetic and molecular studies of acrocentric chromosome polymorphisms was reported by Lorber et al. [1992]. Since cytogenetic heteromorphisms were quite distinct in our case and a study of chiasma distribution in normal male meiosis indicates that crossing-over on the short arms of human acrocentric chromosomes is extremely rare [Laurie and Hultén, 1985], we used cytogenetic heteromorphisms to establish both the parental origin of the extra chromosome and the stage of the meiotic error. As the two number 15 chromosomes in trisomic cells had short arms morphologically identical to the two maternal 15s, and the third 15 unequivocally came from the father, we concluded that primary non-disjunction in our case occurred at maternal meiosis I. Since the diploid cells had chromosome 15 heteromorphisms apparently identical to one maternal and one paternal 15, we concluded that one maternally derived homologue must have been lost in the secondary non-disjunction event, which most likely took place in early postzygotic development. This would produce a diploid and a non-viable tetraploid cell from one of the trisomic cells. An alternative mechanism would be anaphase lag of one chromosome 15. During further development the diploid cell line gained a proliferative advantage over the trisomic cell line.

It was obvious from our studies that the highly heteromorphic 15 was inherited from the father, and that the other paternal 15 was not present in fetal cells. We concluded that the trisomy was maternally derived. However, one can argue that the loss of a maternal 15 occurred in the second nondisjunction event. Since mitotic recombination between acrocentric chromosome short arms is possible, the chromosome 15 with a highly heteromorphic short arm may in fact be of maternal origin. We think this is possible, but not likely in this case.

Cell Selection

Cell selection in vivo has already been described. In two studies on young infants with mosaic Down syndrome, selection against a trisomic cell line was detected during the first year of life [Taylor, 1968; Richards, 1969]. We demonstrate the cell selection against trisomic cells in vivo (the fetus) and in vitro (fetal tissues after freezing and thawing), showing that cell selection can result in elimination of a trisomic cell line.

The lower percentage of trisomic cells in blood lymphocytes than in skin fibroblasts in this fetus is consistent with observations reported previously on patients with mosaic Down syndrome. Ford [1967] concluded that this selective advantage of normal cells is usually more pronounced in tissues with a high mitotic rate such as bone marrow and lymphoid tissues, which give rise to the cells examined in peripheral blood cultures.

The presence of two cell lines (normal and mosaic) in fresh blood and only the normal cell line in frozen transformed blood can be explained by the two different cell populations studied: T-lymphocytes in Phytohemagglutinin (PHA)-stimulated blood cultures and B-lymphocytes in EBV-transformed blood cells. It is possible that the trisomic cell line completely disappeared from B-lymphocytes while it was present in T-lymphocytes from the same blood sample. Alternatively, the transformation process or freezing and thawing (or both) could have contributed to the decline and loss of the trisomic cell line. Since we did not examine chromosomes of transformed cells before freezing, we do not know which of these processes contributed to the disappearance of the trisomic cell line from blood lymphocytes. However, the effect of freezing and thawing on the decline of the trisomic cell line in intestine and skin cultures was evident. Cell selection observed in vitro appears to be a continuation of cell selection initiated in vivo in this fetus.

Clinical Consequences of the Chromosome Loss

Non-disjunction of chromosome 15 leading to trisomy and a subsequent loss of one of the three number 15 chromosomes from the trisomic zygote can have different consequences. The additional chromosome 15 may be lost leading to a normal karyotype with both parental contributions, or the single 15 contributed by one parent may be lost leading to UPD. In either case, a diploid karyotype or mosaicism can result. Which of these will occur depends on which parent contributed the additional chromosome, which of the three number

15 chromosomes was lost during the "normalizing" mitotic error, how soon after fertilization the second nondisjunction took place and whether outgrowth of the trisomic by the normal cell line occurred earlier or later in the postzygotic development.

In our case, the additional chromosome 15 contributed by the mother was the chromosome which was subsequently lost. Clinical abnormalities were due to the trisomic cell line. However, the complete loss of the trisomic line at an early stage might have resulted in a normal fetus.

If a diploid fetal karyotype is derived from a trisomic conceptus one should consider the possibility of uniparental disomy. Furthermore, an early effect of trisomy, or an undetectable degree of mosaicism in the fetus, cannot be ruled out. In addition, the trisomic placenta may have an adverse effect on fetal development resulting in fetal IUGR. Among 17 fetuses with normal karyotypes reported by Kalousek et al. [1991] in which mosaicism was present in the term placenta, six had IUGR. Bennett et al. [1992b] reported a normal karyotype in two infants with IUGR, and Dworniczak et al. [1992] reported one such case. In all three, trisomy 16 mosaicism was present in the placenta. Two of these three infants had uniparental disomy of chromosome 16.

Although trisomy 15 detected at CVS may be confined to the chorion [Kalousek, 1985, Crane and Cheung, 1988] the possibility of true fetal trisomy should also be considered. When trisomy 15 is found at CVS and a normal karyotype at amniocentesis, parents should be counselled about four possibilities in the newborn: normality, mosaicism, UPD, or IUGR. Cytogenetic and molecular techniques are now available to diagnose UPD in a few days. If UPD is ruled out, the risk of abnormality in the newborn due to the presence of undetected trisomic cells will still exist.

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